PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 28053P WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06760	International filing date *(day/month/year)* 26.06.2003	Priority date *(day/month/year)* 26.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/127		
Applicant MUNICH BIOTECH AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.12.2003	27.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Greif, G Telephone No. +49 89 2399-8659

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06760

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-66 as originally filed

Claims, Numbers

1-19 received on 05.05.2004 with letter of 05.05.2004

Drawings, Sheets

1/14-14/14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-19
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
   D1: EP-A-0538 534
   D2: EMERSON D L: "Liposomal delivery of camptothecins" PHARMACEUTICAL SCIENCE AND TECHNOLOGY TODAY, ELSEVIER TRENDS JOURNALS, CAMBRIDGE,, GB, vol. 3, no. 6, 1 June 2000 (2000-06-01), pages 205-209,

2. **Novelty**

document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and shows camptothecin isolated in the carboxylate form, where the hydrolysis took place in presence of organic hydroxides such as tetraalkylammonium hydroxyde.
The subject-matter of claim 1 differs from the subject-matter of D1 in that the composition does not comprise an anionic amphiphile and/or cationic polymer having a positive net charge.
The subject-matter of claim 1 and dependent claims 2-6 are therefore novel.
Novelty is also acknowledged for claims 7-15, a nanoaggregate comprising the composition of claim 1, and claims 17 and 18, a method of preparation of the nanoaggregate of claim 7.

D1 differs from claim 16, a pharmaceutical preparation comprising the carboxylate form of a camptothecin drug associated with an organic cationic molecule, since D1 does not refer to the pharmaceutical use of the carboxylate form of camptothecin, said form merely being an intermediate step to increase the yield of the lactone form (believed to be the active form in the state io the art). Novelty is also acknowledged for claim 19, the use of said pharmaeutical preparation for producing a medicament for the treatment of a disease.

3. **Inventive Step**

The problem to be solved by claim 1 may be regarded as providing an alternative camptothecin preparation.
The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

There is no document teaching the addition of a cationic amphiphile as claimed. In the light of D1, it would not be obvious for the expert to replace the organic hydroxide with such a compound. Claims 1-15 and 17 and 18 are thus inventive.
The problem to be solved by claim 16 can be regarded as providing an alternative pharmaceutical camptothecin preparation. The solution consists of pharmaceutical compositions comprising campthotecin in the carboxylate form.
Since the prior art teaches away from the use of the carboxylate form of camptothecin as a medicament, the lactone form being the accepted form (see D2). Claims 16 and 19 are therefore considered to be inventive.

4. Industrial applicability

For the assessment of the present claim 19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

New Claims 1 to 19

1. A composition comprising the carboxylate form of a camptothecin drug associated with at least one cationic amphiphile and/or cationic polymer having a positive net charge wherein the molar ratio of the organic cationic molecule to the carboxylate and is at least about 1:1 wherein said composition is substantially free of the lactone form of said camptothecin.

2. The composition of claim 1, wherein said cationic amphiphile is selected from lipids, lysolipids or pegylated lipids, preferably having a tertiary amino or quaternary ammonium group such as N-[1-(2,3-diacyloxy)propyl]-N,N-dimethylamine or N-[1-(2,3-diacyloxy)propyl]-N,N,N-trimethyl ammonium.

3. The composition of any one of claims 1 or 2, wherein said cationic polymer is a polyelectrolyte, acid such as polyallylamine or polyethylene imine, a polymeric sugar or a polyamine with a molecular weight between about 5 and about 500 kDa.

4. The composition of any one of the claims 1 to 3, further comprising at least one anionic and/or neutral amphiphile.

5. The composition of any one of claims 1 to 4, wherein said anionic and/or neutral amphiphile is selected from sterols or lipids such as cholesterol, phospholipids, lysolipids, lysophospholipids, sphingolipids or pegylated lipids with a negative or neutral net change.

6. The composition of any one of the claims 4 to 5, wherein the neutral amphiphile is diacylphosphatidylcholine.

7. A colloidal nanoaggregate comprising a composition of any one of the claims 1 to 6.

8. The nanoaggregate of claim 7 having an overall positive charge.

9. The nanoaggregate of claim 7 or 8, further comprising at least one amphiphile which has a negative and/or neutral net charge (anionic and/or neutral amphiphile).

10. The nanoaggregate of any one of the claims 7 to 9, wherein said anionic and/or neutral amphiphile is selected from sterols or lipids such as cholesterol, phospholipids, lysolipids, lysophospholipids, sphingolipids or pegylated lipids with a negative or neutral net change.

11. The nanoaggregate of any one of the claims 7 to 10, wherein the neutral amphiphile is diacylphosphatidylcholine.

12. The nanoaggregate of any one of the claims 7 to 11, comprising an excess of positively charged moieties of at least about 20 %, preferably at least about 30 % and most preferably at least about 40 % in the outer molecular layer.

13. The nanoaggregate of any one of the claims 7 to 12, which is present as an emulsion droplet, a micelle, a liposome, a nanoparticle or a nanocapsule.

14. The nanoaggregate of any one of the claims 7 to 13, comprising about 0.1 to about 50 mol% of a camptothecin drug or a derivative thereof.

15. The nanoaggregate of any one of the claims 7 to 14, further comprising a cryoprotectant which is selected from a sugar or an alcohol or a combination thereof such as trehalose, maltose, sucrose, glucose, lactose, dextran, mannitol or sorbitol.

16. A pharmaceutical preparation comprising a pharmaceutically effective amount of a composition comprising the carboxylate form of a camptothecin drug associated with at least one organic cationic molecule having a positive net charge wherein the molar ratio of the organic cationic molecule to the carboxylate and is at least about 1:1 wherein said composition is substantially free of the lactone form of said camptothecin, or a colloidal nanoaggregate thereof, together with a pharmaceutically acceptable carrier, diluent and/or adjuvant.

17. A method of producing the colloidal nanoaggregate of any one of the claims 7 to 15, comprising the steps of

a) providing a camptothecin drug, preferably as a salt,

b) associating said camptotecin drug in its carboxylate form with a cationic amphiphile having a positive net charge and optionally at least one further amphiphile which has a positive, negative and/or neutral net charge, and

c) forming a colloidal nanoaggregate.

18. The method of claim 17, wherein step b) and c) comprise forming said nanoaggregate by a homogenisation, a lipid film or by a solvent injection procedure.

19. The use of a pharmaceutical preparation of claim 16 for producing a medicament for treating and/or preventing a disease characterized by enhanced angiogenic activity.

kt 28.04.2004